Alipogene tiparvovec (AMT-011, Glybera) for lipoprotein lipase deficiency

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Alipogene tiparvovec (Glybera) for lipoprotein lipase deficiency

Target group
- Lipoprotein lipase deficiency - also known as familial chylomicronaemia or hyperlipoproteinaemia type I.

Background
Lipoprotein lipase deficiency (LPLD) is an inherited metabolic disorder, characterised by abnormally elevated plasma concentrations of chylomicrons and triglycerides. LPLD includes patients classified as having hyperlipoproteinaemia type 1 (also known as familial chylomicronaemia) due to a deficiency of lipoprotein lipase (LPL) and those with a deficiency of apolipoprotein C-II, a lipase activating protein. LPL hydrolyses the triglyceride component of circulating chylomicrons and very low density lipoproteins (VLDL). When LPL activity is reduced, chylomicrons accumulate within the bloodstream and cause symptoms such as: abdominal pain, an enlarged spleen and liver, eruptive xanthomas and potentially lethal pancreatitis.

The gene encoding for LPL is located on chromosome 8 and is expressed mainly in skeletal muscle, adipose tissue, and heart muscle.

Technology description
Alipogene tiparvovec (AMT-011, Glybera) is an adeno-associated viral vector (AAV1) based gene therapy, administered intramuscularly (IM) at multiple-sites in a single session. AAV1 carrying the human variant LPL$^{S447X}$ gene is delivered to skeletal muscle, where it becomes active. The LPL protein is expressed and transported to the capillary endothelium where it binds to chylomicrons and VLDL. Alipogene tiparvovec is intended as a curative measure for patients with LPLD and, as well as enhancing chylomicron metabolism, may prevent episodes of pancreatitis.

Innovation and/or advantages
If licensed, alipogene tiparvovec will be the first therapy to potentially cure LPLD.

Developer
Amsterdam Molecular Therapeutics (AMT) B.V.

Availability, launch or marketing dates, and licensing plans:
Alipogene tiparvovec is a designated orphan drug in the EU. The company anticipate a Marketing Authorisation Application with the EMEA in Q3/4 2009.

NHS or Government priority area
This topic is relevant to The National Service Framework for Diabetes (2007), as many patients develop diabetes.

Relevant guidance
No relevant guidance on LPLD was identified.

Clinical need and burden of disease
LPLD is a very rare disorder with no data identified on the incidence and prevalence in the UK. It is estimated that approximately 1 in 1,000,000 people are affected in populations, which equates to approximately 52 people in England and Wales\(^1\). Prognosis
is thought to be relatively good when a very low fat diet is maintained with early mortality and morbidity mainly due to recurrent pancreatitis; these patients are also at risk of developing diabetes mellitus. A number of acquired conditions such as kidney and liver disease, alcoholism and diabetes mellitus may also raise triglyceride levels. There is debate about how closely LPLD is associated with accelerated atherosclerosis and increased cardiovascular risk independent of diabetes. 

**Existing comparators and treatments**

Currently there is no effective treatment or cure for LPLD. The primary objective is to reduce pancreatitis by preventing chylomicronaemia.

Patients must follow a lifetime diet with extremely low fat intake at less than 20g per day (<10% of total daily intake in calories). A 20g to 40g per day medium-chain triglyceride diet may be used to supplement calorie intake.

Pharmacological treatment options include statins, nicotinic acid, fibrates and fish oils (no evidence of specific benefit in patients with LPLD). Fat soluble vitamins A, D, E and K and mineral supplements are recommended.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT-AMT-010; LPLD; phase II with 5 year extension.</th>
<th>CT-AMT-011-01; LPLD; phase II/III, with long term follow up.</th>
<th>NCT008913064: Alipogene Tiparvovec; phase II/III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AMT.</td>
<td>AMT.</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Status</td>
<td>Conference abstract⁵,⁶.</td>
<td>Conference abstracts⁷,⁸ interim results.</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Location</td>
<td>Netherlands.</td>
<td>Canada.</td>
<td>Canada</td>
</tr>
<tr>
<td>Design</td>
<td>Open label, dose escalating.</td>
<td>Open label.</td>
<td>Open label, non-controlled.</td>
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<td>Participants and schedule</td>
<td>n=8; adults; LPLD (LPL activity ≤ 20%, LPL mass &gt;5% of normal, TG levels &gt; 10mmol/L). Randomised to AMT-010 1x10ⁱ¹ gc/kg (n=4) or AMT-010 3x10⁵ gc/kg (n=4) intramuscular (IM) administration.</td>
<td>n=14; adults; LPLD. Randomised to AMT-011 1x10¹² gc/kg and immunosuppression or AMT-011 3x10¹¹ gc/kg or AMT-011 3x10¹¹ gc/kg and immunosuppression.</td>
<td>n=8 (planned); adults; LPLD (LPL activity ≤ 20%, TG levels &gt; 10mmol/L); previous pancreatitis. Received AMT-011 1x10¹² gc/kg with mycophenolate mofetil and cyclosporine (for 12 weeks) and IV methylprednisolone (single dose).</td>
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<td>Follow-up</td>
<td>12 week initial observation period with 5 years long term follow up.</td>
<td>12 week initial observation period with 15 years long term follow up.</td>
<td>12-14 week treatment period with 1 year extension.</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>Median fasting triglycerides (TG) ≤10 mmol/L or a ≥40% reduction on top of a fat free diet.</td>
<td>Triglycerides (TG) levels; metabolic indicators; serious adverse events; viral shedding.</td>
<td>TG levels.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>LPL protein mass &amp; activity; immune response. Safety including</td>
<td>Reduction of chylomicrons and/or chylomicron-TG ratio; safety.</td>
<td></td>
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<td>Key results</td>
<td>At 12 weeks all patients had reduced median TG level (p&lt;0.007), with a mean reduction of 27% and 41% for AMT-010 1x10¹¹ gc/kg and 3x10¹¹ gc/kg. Pancreatitis events reduced from 0.49 to 0.04 episodes per year per patient. At 18 to 31 months TG levels were not significant reduced from baseline.</td>
<td>At end of year 1 no episodes of pancreatitis reported. Fat accumulations in skin or retina disappeared or reduced. In 2 diabetic patients, reduction of insulin resistance observed. All patients reported increase in energy.</td>
<td></td>
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<td>Adverse effects</td>
<td>No serious AE’s observed.</td>
<td>One episode of pancreatitis immediately after injection not judged to be related to interventional therapy.</td>
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</tbody>
</table>

### Estimated cost and cost impact
The cost of alipogene tiparvovec is not yet known.

### Potential or intended impact – speculative
Although alipogene tiparvovec has potential to make a significant impact in patients with LPLD the requirement for patients to receive ongoing immunosuppression is uncertain. Patients will still need to adhere to a lipid-restricted diet.

| Patients                                                                                          | Reduced morbidity | Reduced mortality or increased length of survival | Improved quality of life for patients and/or carers | None identified |
| Services                                                                                         | Increased use | Service reorganisation required | Staff or training required | None identified |
| Costs                                                                                           | Increased unit cost compared to alternative | New costs: addition to current therapy and requires 3 months of immunosuppressive therapy | Increased costs: more patients coming for treatment | Increased costs: capital investment needed |


8 Gaudet D, Brisson D, Methot J et al. An open-label, dose escalation study to assess the safety and efficacy of AAV1-LPL.ene therapy with alipogene tiparvovec, AMT-011) for patients with severe hypertriglyceridemia due to lipoprotein lipase deficiency (LPLD). Atherosclerosis Supplements 2009;10 (s) Abstract 554.